



# Semeiology of the hematopoietic system disorders

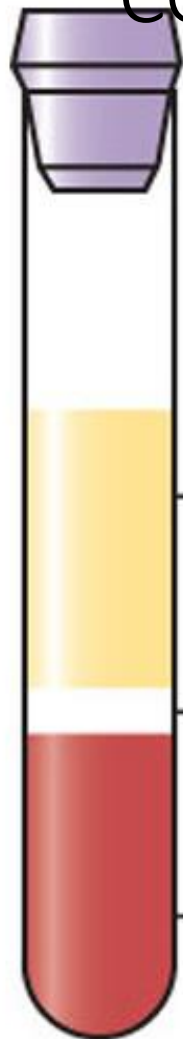
**Department of Pediatrics**

Olga CÎRSTEA, MD, PhD,  
Associate Professor

# What is hematology?

- Hematology is the study of blood which is composed of plasma (~55%), and the formed elements which are:
  - The erythrocytes (RBCs) (~45%)
    - Contain hemoglobin
    - Function in the transport of  $O_2$  and  $CO_2$
  - The Leukocytes (WBCs) and platelets (thrombocytes) (~1%)
    - Leukocytes are involved in the body's defense against the invasion of foreign antigens.
    - Platelets are involved in hemostasis which forms a barrier to limit blood loss at an injured site.

# COMPOSITION OF BLOOD



Plasma  $\left\{ \begin{array}{l} \text{Water (91.5\%)} \\ \text{Proteins (7\%)} \\ \text{Other Solutes (1.5\%)} \end{array} \right.$

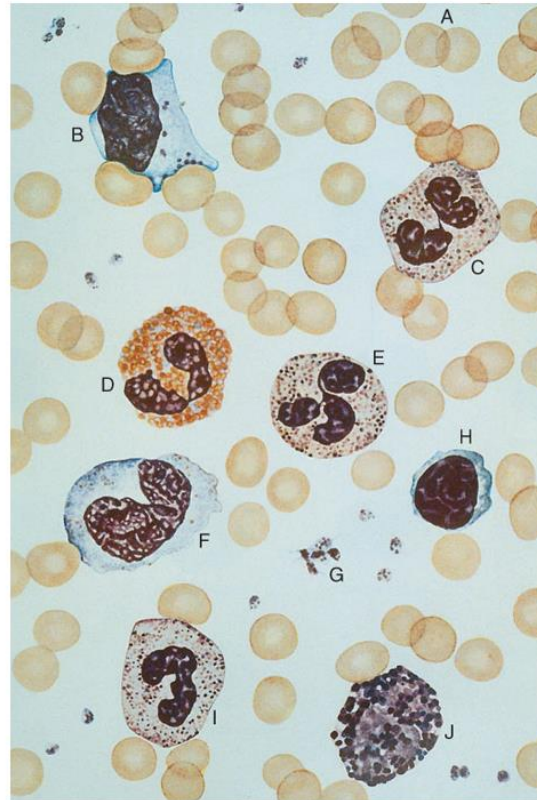
"Buffy Coat"  
White Blood Cells  
Platelets

Red Blood Cells

Lymphocytes  
Granulocytes  
Monocytes

Basophils  
Neutrophils  
Eosinophils

# TYPES OF FORMED ELEMENTS IN THE BLOOD



- Hematology is primarily a study of the formed cellular elements.
- Alterations in the formed elements in the blood are usually a **result of disease** rather than being the primary cause of disease.
  - In fact, variations in the formed elements in the blood are often the **first sign** that disease is occurring in the body.
  - The changes caused by disease may be detected by lab tests that measure deviations of the blood constituents from the normal values. These lab test may include:

- RBC count
  - WBC count
  - Platelet count
  - Hematocrit (packed cell volume)
  - Mean corpuscular volume (MCV)
  - Mean corpuscular hemoglobin concentration (MCHC)
- Under normal conditions the production, release, and survival of blood cells is a highly regulated process. Quantitative and/or qualitative hematologic abnormalities may result when there is an **imbalance between cell production, release, and/or survival.**

- Age, sex, and geographic location are involved in **physiologic changes** in normal values of the formed cellular elements
- **Pathologic changes** in the values of the formed cellular elements occur with disease or injury.
- Normal values for a group are determined by calculating the mean for healthy individuals of the group and reporting the normal range as the mean  $\pm$  2 standard deviations

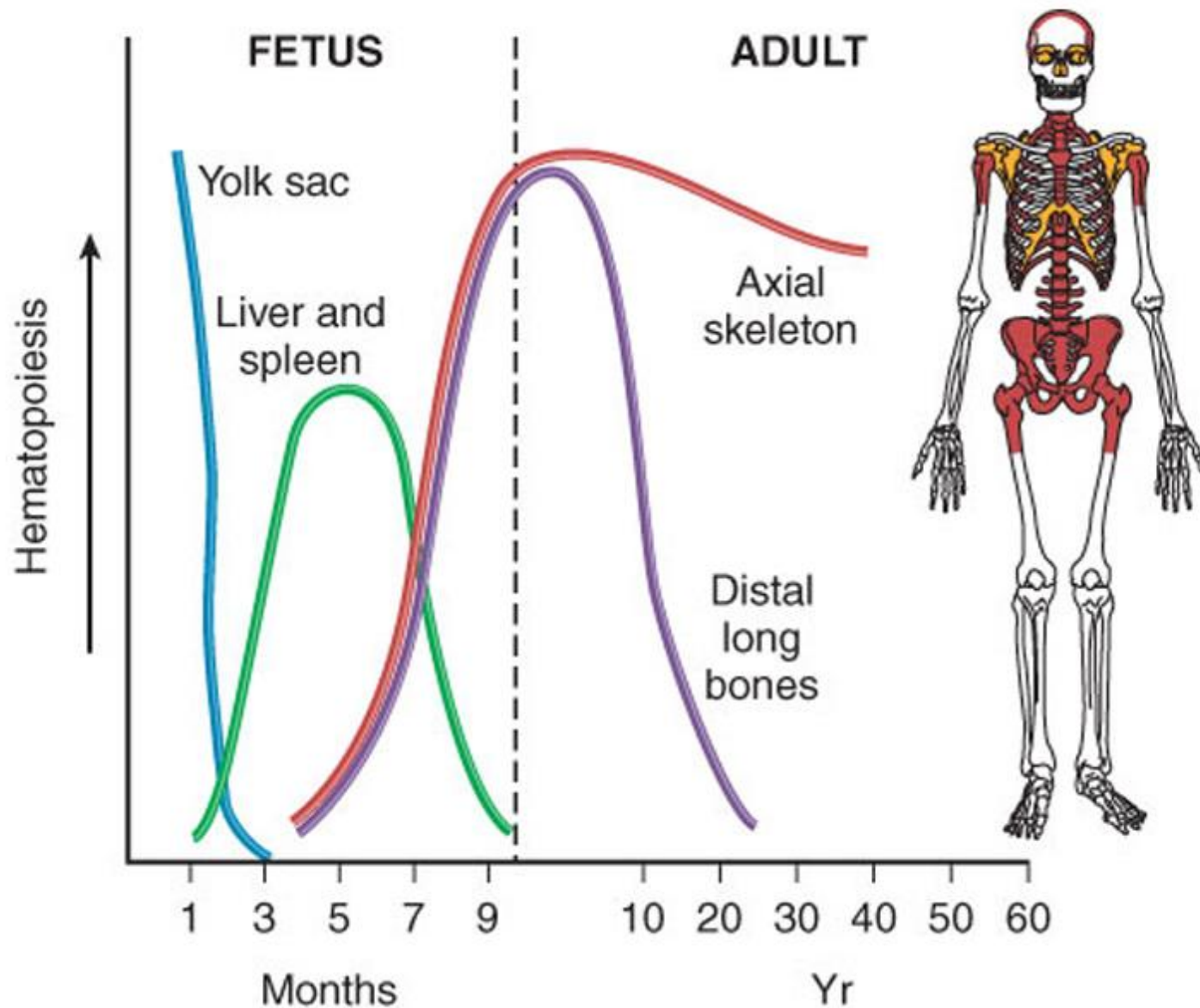
# Hematopoiesis

- A term describing the formation and development of blood cells.
  - Cells of the blood are constantly being lost or destroyed. Thus, to maintain homeostasis, the system must have the capacity for self renewal. This system involves:
    - Proliferation of progeny stem cells
    - Differentiation and maturation of the stem cells into the functional cellular elements.



- Hematopoiesis begins as early as the nineteenth day after fertilization in the **yolk sac of the embryo**
  - Only erythrocytes are made
  - The RBCs contain unique **fetal hemoglobins**
- At about 6 weeks of gestation, yolk sac production of erythrocytes decreases and production of RBCs in the human embryo itself begins.

- The fetal liver becomes the chief site of blood cell production.
  - Erythrocytes are produced
  - The beginnings of leukocyte and thrombocyte production occurs
- The spleen, kidney, thymus, and lymph nodes serve as minor sites of blood cell production.
- The lymph nodes will continue as an important site of lymphopoiesis (production of lymphocytes) throughout life, but blood production in the other areas decreases and finally ceases as the bone marrow becomes the primary site of hematopoiesis at about 6 months of gestation and continues throughout life.
  - When the bone marrow becomes the chief site of hematopoiesis, leukocyte and thrombocyte production become more prominent.



# Hematopoiesis

- Hematopoiesis in the bone marrow is called **medullary hematopoiesis**
- Hematopoiesis in areas other than the bone marrow is called **extramedullary hematopoiesis**
  - Extramedullary hematopoiesis may occur in fetal hematopoietic tissue (liver and spleen) of an older child when the bone marrow cannot meet the physiologic needs of the tissues. This can lead to hepatomegaly and/or splenomegaly (increase in size of the liver and/or spleen because of increased functions in the organs).
- **Hematopoietic tissue** includes tissues involved in the proliferation, maturation, and destruction of blood cells

- The mononuclear phagocytic system (also called the **reticular endothelial system** or **RES**) is involved in **cellular destruction** and it includes:
  - Circulating blood monocytes
  - Fixed macrophages in the bone marrow, liver, spleen, and lymph nodes
  - Free macrophages
    - These cells are involved in:
      - Engulfing particulate matter
      - Processing of antigens for lymphocyte presentation
      - Removal of damaged or senescent (aged) cells

- **Spleen** – contains the largest collection of lymphocytes and mononuclear phagocytes in the body. The spleen functions in:
  - Filtering and destruction of senescent (aged) or damaged RBCS – also called **culling**
  - Removal of particles (are found in some types of anemia) from RBC membranes – also called **pitting** – this causes a decrease in the surface to volume ratio of the RBC resulting in the formation of spherocytes (more on this later)
  - Enforcing close contact of blood borne antigens with lymphocytes and phagocytic cells – this is more important in children particularly in protection of the host from infections due to **enveloped organisms**

- Sequestering 1/3 of the platelet mass – in massive splenomegaly this can lead to peripheral **thrombocytopenia** (decrease in platelets in the peripheral blood)
- After a **splenectomy** (removal of the spleen), RBC inclusions and abnormal RBC shapes are seen. Culling is taken over by the liver which is less effective in performing all of the splenic functions
- **Hypersplenism** (splenomegaly) – in a number of conditions the spleen may become enlarged and through an exaggeration of its normal functions of filtering, and destruction and sequestering, it may cause **anemia** (may be caused by decreased RBCs), **leukopenia** (decreased WBCs), or **thrombocytopenia** or combinations of these cytopenias. When all three cell types are decreased this is called **pancytopenia**.

# There are two types of hypersplenism:

- Primary – no underlying disease has been identified
- Secondary – caused by an underlying disorder such as:
  - Inflammatory diseases
  - Infectious diseases
  - Blood disorders that cause compensatory or workload hypertrophy of the organ such as:  
Abnormal blood cells, antibody coated blood cells, hereditary spherocytosis, idiopathic thrombocytopenic purpura (ITP)
- The effects of these are relieved by splenectomy



- **Lymph nodes** – the lymphatic system is composed of lymph nodes and lymphatic vessels that drain into the left and right lymphatic duct. Lymph is formed from blood fluid that escapes into the connective tissue.
  - Lymph nodes are composed of lymphocytes, macrophages, and a reticular network.
  - They act as filters to remove foreign particles by phagocytic cells
  - As antigens pass through the lymph nodes, they come into contact with and stimulate immunocompetent lymphocytes to proliferate and differentiate into effector cells.

- The structure of the lymph node consists of:
  - An inner area called the medulla which contains **plasma cells**
  - An outer area called the cortex which contains **follicles** with B lymphocytes surrounded by T lymphocytes and macrophages

- **Thymus** – this organ is well developed at birth and increases in size until puberty at which time it starts to decrease in size.
  - It serves as a compartment for the **maturation of T lymphocytes** into immunocompetent T cells. The hormone thymosin plays a role in this process.
  - The structure of the thymus consists of:
    - An outer area called the **cortex** which is densely packed with small lymphocytes and macrophages
    - An inner area called the **medulla** which is less cellular with a few lymphocytes, macrophages, and epithelial cells.

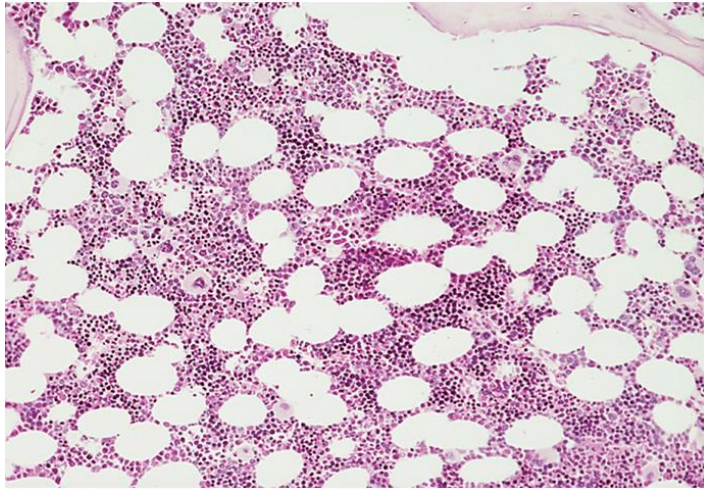
## Bone marrow – is located inside spongy bone

- In a normal adult,  $\frac{1}{2}$  of the bone marrow is hematopoietically active (**red marrow**) and  $\frac{1}{2}$  is inactive, fatty marrow (**yellow marrow**).
- The marrow contains both Erythroid (RBC) and leukocyte (WBC) precursors as well as platelet precursors.
- Early in life most of the marrow is red marrow and it gradually decreases with age to the adult level of 50%.
- In certain pathologic states the bone marrow can increase its activity to **5-10X** its normal rate.
  - When this happens, the bone marrow is said to be **hyperplastic** because it replaces the yellow marrow with red marrow.

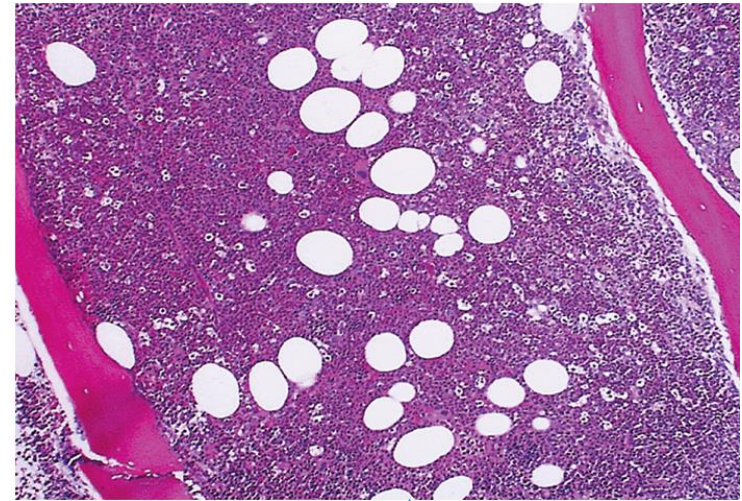
- This occurs in conditions where there is **increased or ineffective hematopoiesis**.
- The degree to which the bone marrow becomes **hyperplastic** is related to the severity and duration of the pathologic state.
- Pathologic states that cause this include:
  - Acute blood loss in which there is a temporary replacement of the yellow marrow
  - Severe chronic anemia – erythropoiesis (RBC production) may increase to the extent that the marrow starts to erode the bone itself.
  - Malignant disease – both normal red marrow and fatty marrow may be replaced by proliferating abnormal cells.

- The hematopoietic tissue may also become inactive or **hypoplastic**. This may be due to:
  - Chemicals
  - Genetics
  - Myeloproliferative disease that replaces hematopoietic tissue with fibrous tissue

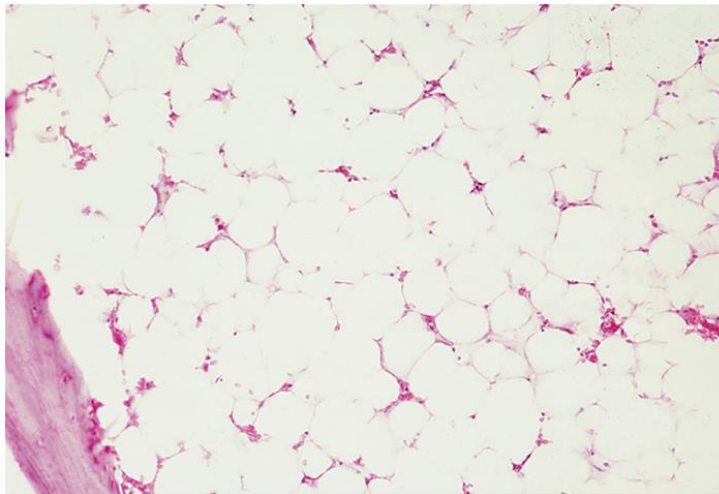
# BONE MARROW



Normal



Hyperplastic

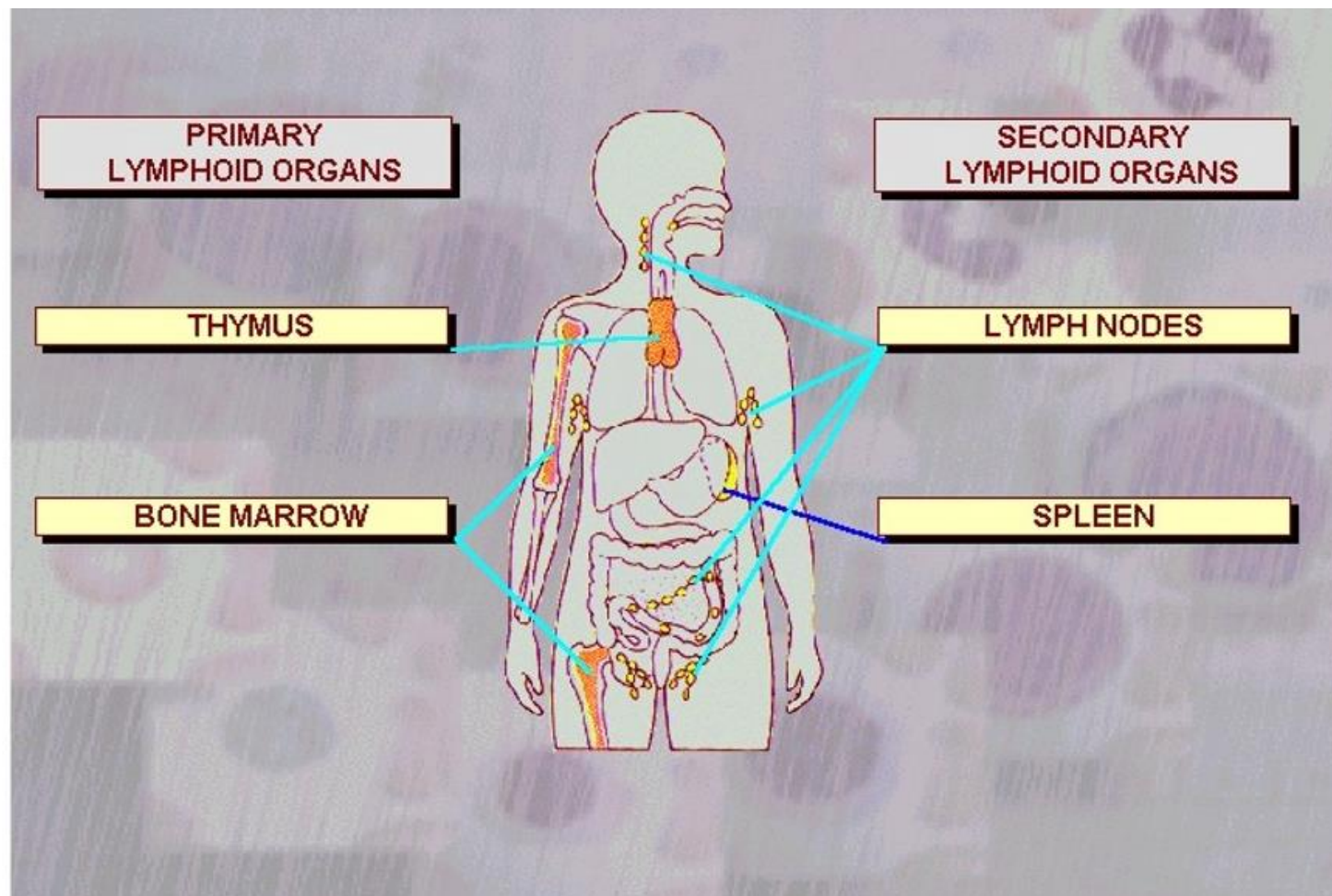


Hypoplastic

- **Liver** – contains phagocytic cells known as Kupffer cells that act as a filter for damaged or aged cells in a manner similar to, but less efficient than the phagocytic cells in the spleen.
  - If the bone marrow cannot keep up with the physiologic demand for blood cells, the liver may resume the production of blood cells that it began during fetal life



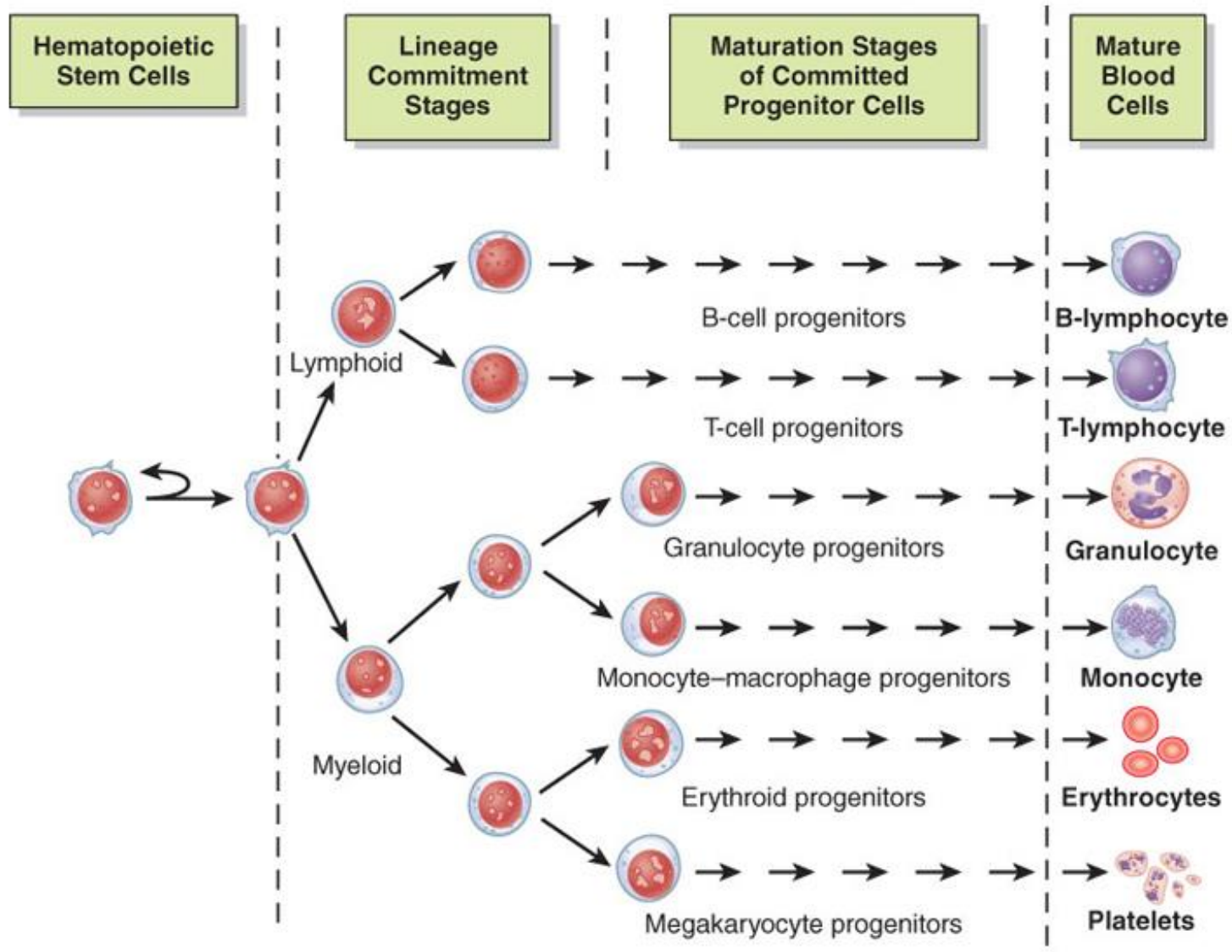
# Summary of blood forming organs



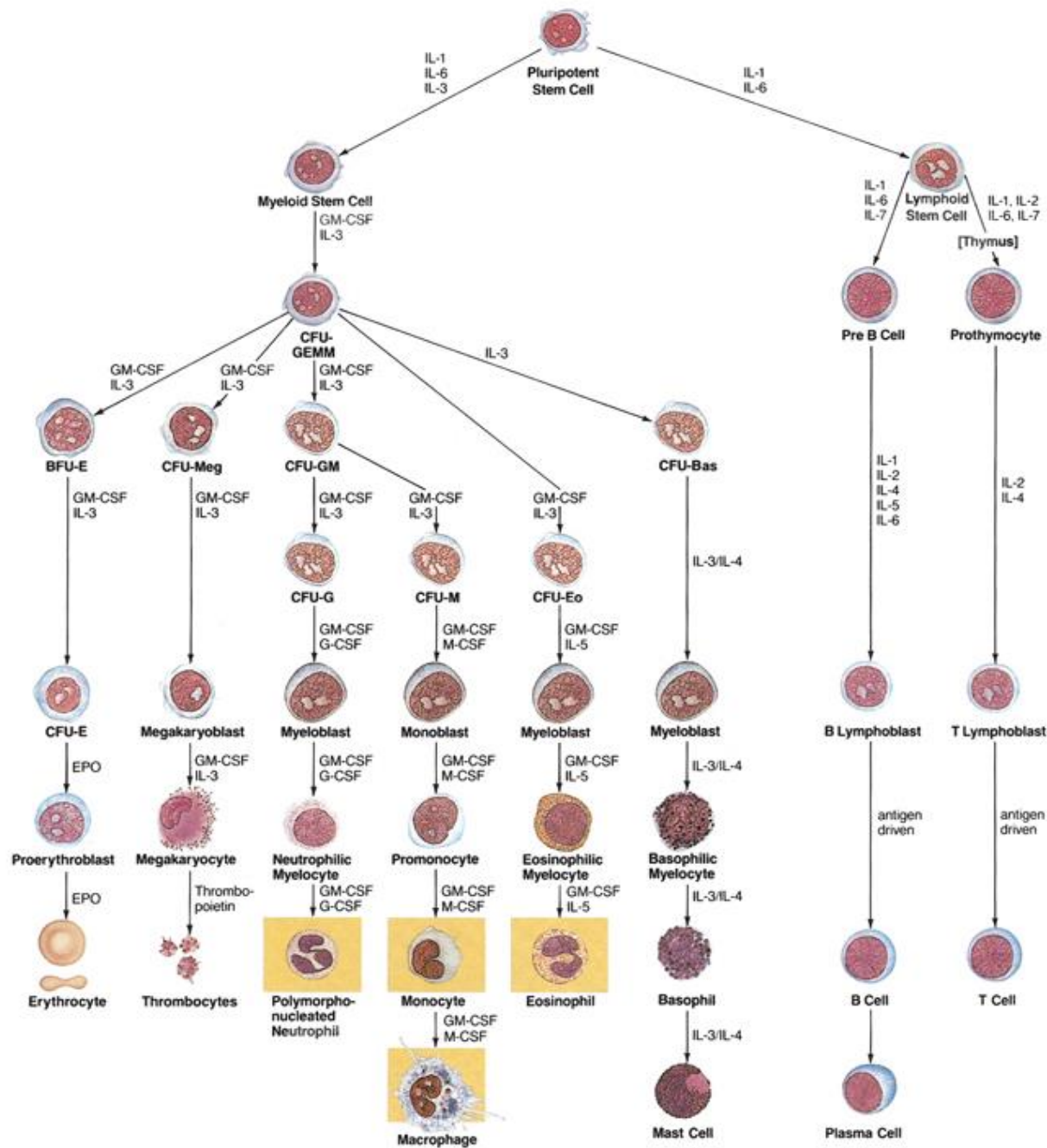
# Derivation of blood cells

- Mature blood cells have a limited life span and with the exception of lymphocytes, are incapable of self-renewal.
  - Replacement of peripheral hematopoietic cells is a function of the **pluripotential (totipotential) stem cells** found in the bone marrow
    - Pluripotential stem cells can differentiate into all of the distinct cell lines with specific functions and they are able to regenerate themselves.
    - The pluripotential stem cells provide the cellular reserve for the stem cells that are committed to a specific cell line.

- The committed lymphoid stem cells will be involved in lymphopoiesis to produce lymphocytes
  - The committed myeloid stem cell can differentiate into any of the other hematopoietic cells including erythrocytes, neutrophils, eosinophils, basophils, monocytes, macrophages, and platelets.
- Hematopoietic cells can be divided into three cellular compartments based on maturity:
    - **Pluripotential stem cell** capable of self-renewal and differentiation into all blood cell lines.
    - **Committed progenitor stem cells** destined to develop into distinct cell lines
    - **Mature cells** with specialized functions



# Hematopoiesis



# DIANOSTIC APPROACH TO Pediatric Coagulation Disorders



# Objectives

- 1. To describe the physiology of hemostasis in the pediatric patient.
- 2. To list clinical signs and symptoms suggestive of a congenital or acquired bleeding disorder.
- 3. To understand laboratory testing and indications in the diagnosis of a bleeding disorder.

# PATHOPHYSIOLOGY OF HEMOSTASIS

- Hemostasis is a complex process that requires a balance between maintaining blood in a fluid state and addressing areas of tissue injury in which a local response is generated at the site of vascular endothelial injury to promote healing and prevent hemorrhage.
- This process requires the interaction of the vascular endothelium, platelets, and coagulation factors.



# PATHOPHYSIOLOGY OF HEMOSTASIS

- Diminished or dysfunctional activity of any of the components of the hemostatic system leads to coagulopathy, and different bleeding or thrombotic manifestations depend on the severity or lack of function of a particular hemostatic component.

# HEMOSTASIS

- The hemostatic process is initiated at the site of tissue or vascular injury.
- The disrupted vascular endothelial cells, exposed subendothelial connective tissue, and smooth muscle activate their procoagulant properties with the release of von Willebrand factor (vWF), which allows platelet binding (primary hemostasis).

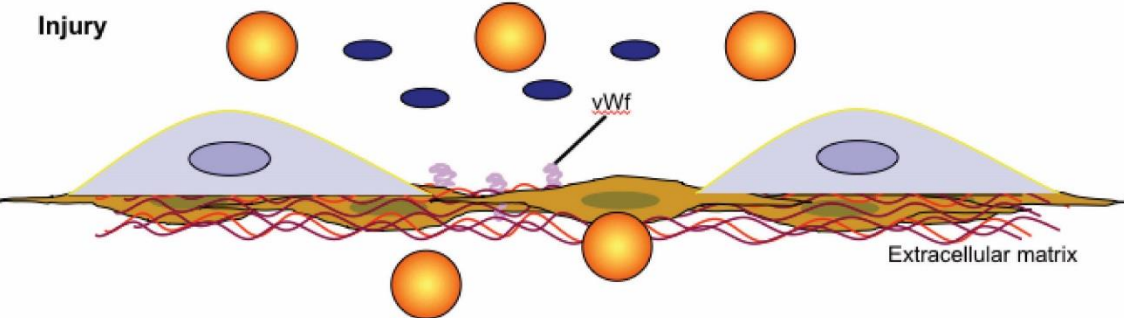
# HEMOSTASIS

- Platelets are anucleate discoid cells (normal size 0.5–3.0  $\mu$ m) that contain granules with procoagulant factors and surface receptors that enable their attachment to the damaged endothelium.
- Three phases traditionally describe platelet activation: **adhesion**, **activation**, and **aggregation**.
- Through adhesion, platelets attach to the damaged endothelium with the help of cell surface receptors (mediated through glycoprotein [GP]Ib-IX-V receptor).

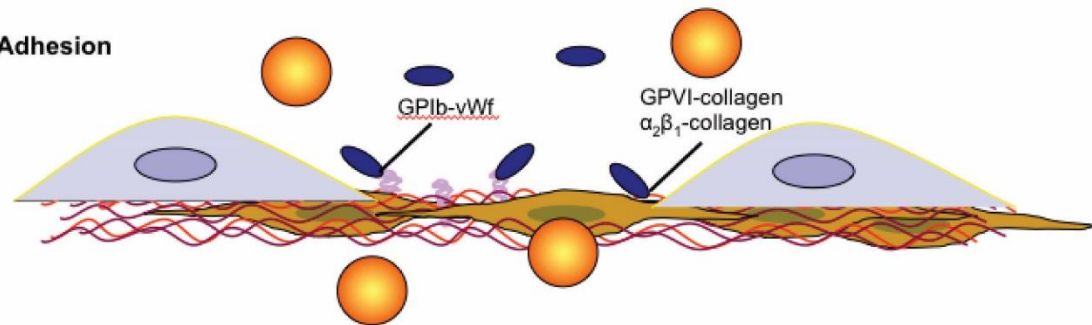
# HEMOSTASIS

- Once attached to the endothelium, platelets are activated via intracellular signaling mechanisms, resulting in granule release.
- The released substances constitute chemotactic factors (adenosine diphosphate [ADP] and thromboxane A<sub>2</sub>) and cofactors for the intrinsic pathway of coagulation cascade and fibrin formation, leading to platelet aggregation (platelet interaction with vWF and platelet-to-platelet binding mediated by GPIIb-IIIa receptor, secondary hemostasis).

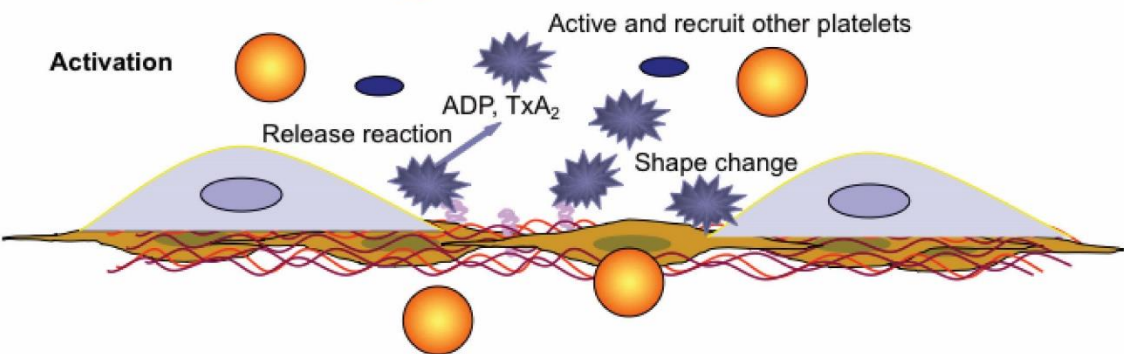
## Injury



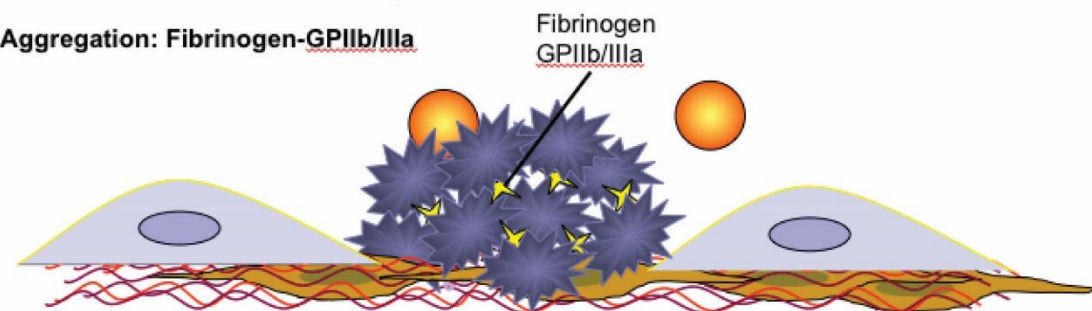
## Adhesion



## Activation



## Aggregation: Fibrinogen-GPIIb/IIIa



**The primary platelet plug**

# HEMOSTASIS

- Tissue factor binds to factor VII (FVII) (**extrinsic pathway**) and with the help of platelet-derived phospholipids, calcium, further activates factor X (FX).
- FX interacts with factor V (FV), prothrombin, calcium, and phospholipids, ultimately generating thrombin.
- Thrombin can generate further thrombin through activation of the contact factor pathway (**intrinsic pathway**) via positive feedback.

# HEMOSTASIS

- Both pathways interact and provide several feedback loops to augment the activity or cause enzymatic activation of several of the coagulation components.
- Both pathways converge in the common pathway, with activation of FX resulting in the conversion of fibrinogen into fibrin, along with factor XIII (FXIII) activation that crosslinks fibrin for better clot stabilization.

# NORMAL COAGULATION PATHWAYS

## **Intrinsic pathway** clotting factors

Factor XII	Factor IX
Factor VIII	Factor XI

## **Extrinsic pathway** clotting factors

Tissue factor (blood vessel injury exposes TF, normally it is not present in plasma)

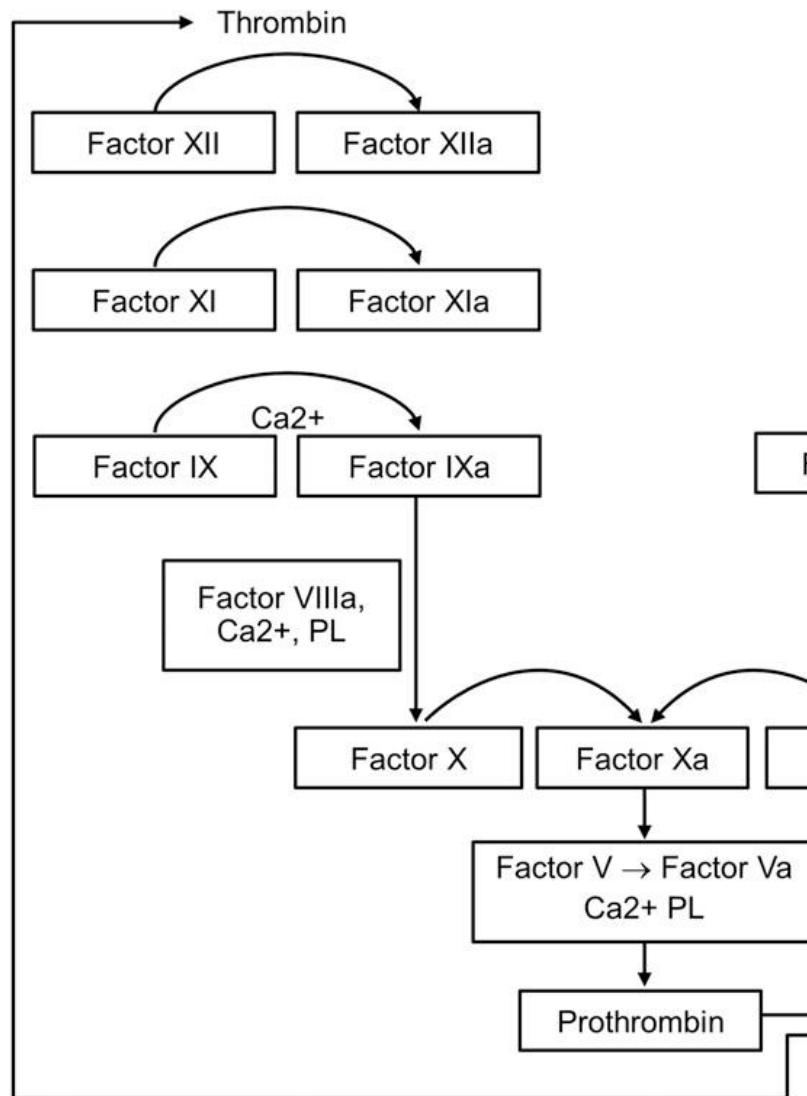
Factor VII

## **Common pathway** clotting factors

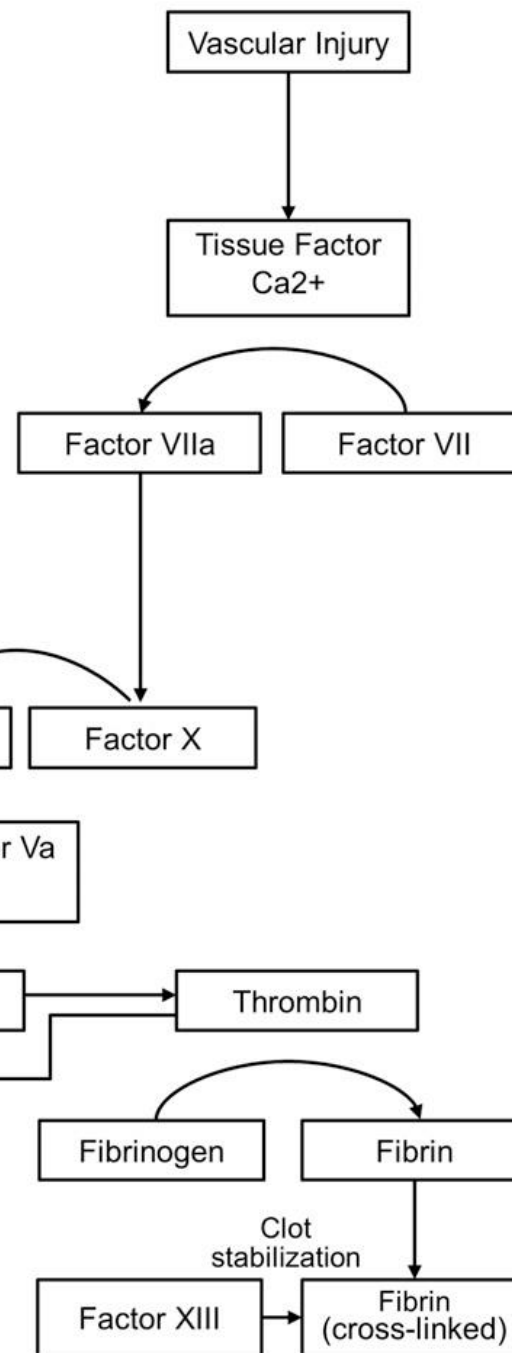
Factor X	
Factor V	
Factor II	Prothrombin
Factor I	Fibrinogen



## Intrinsic Pathway



## Extrinsic Pathway



## Intrinsic pathway

XII ----> XIIa

XI-----XIIa  
v

IX -----> IXa  
v

+ VIII  
v

X-----> Xa

## Extrinsic pathway

VII + TF -----> VIIa/TF

v

IXase ("crossover")  
Xase (minor)

[Common pathway]

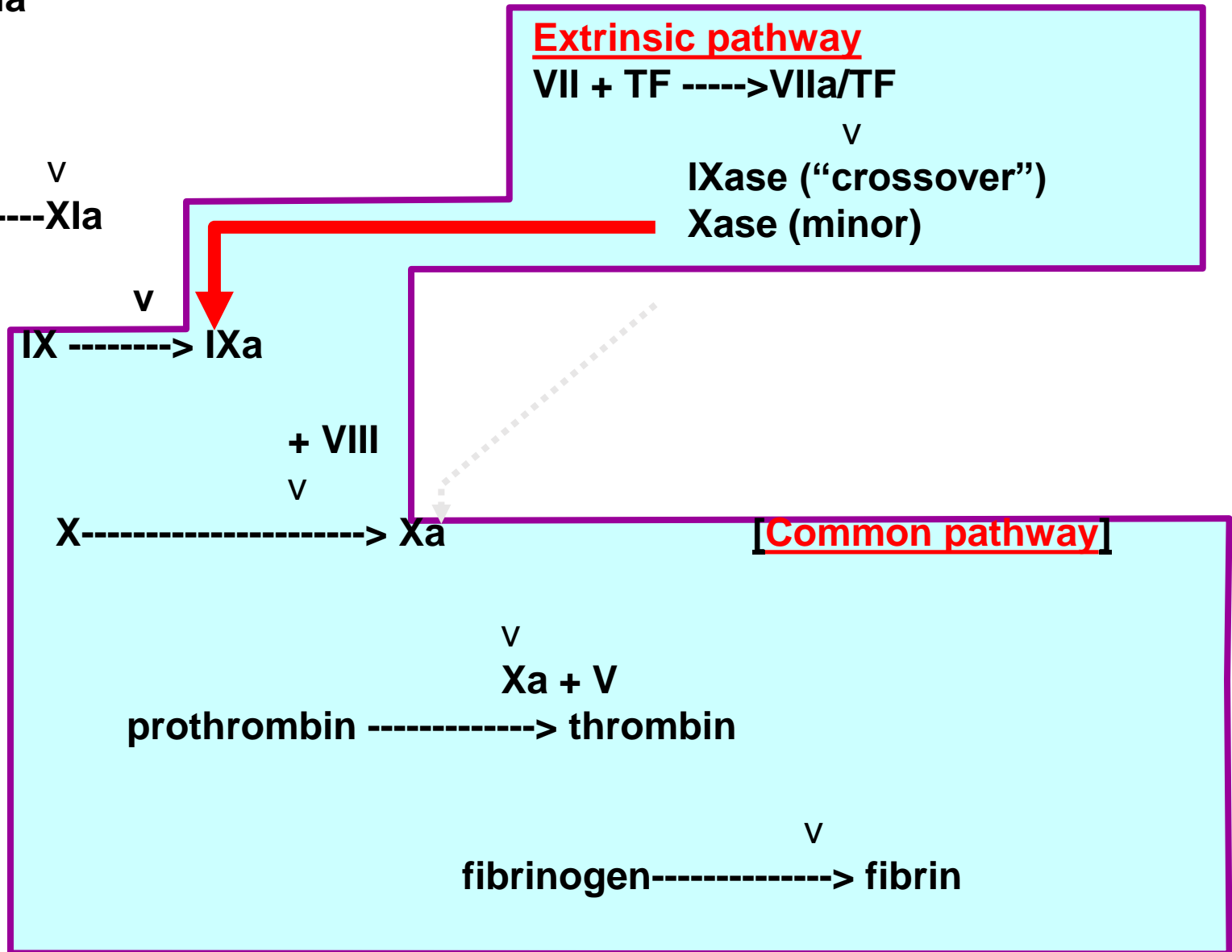
v

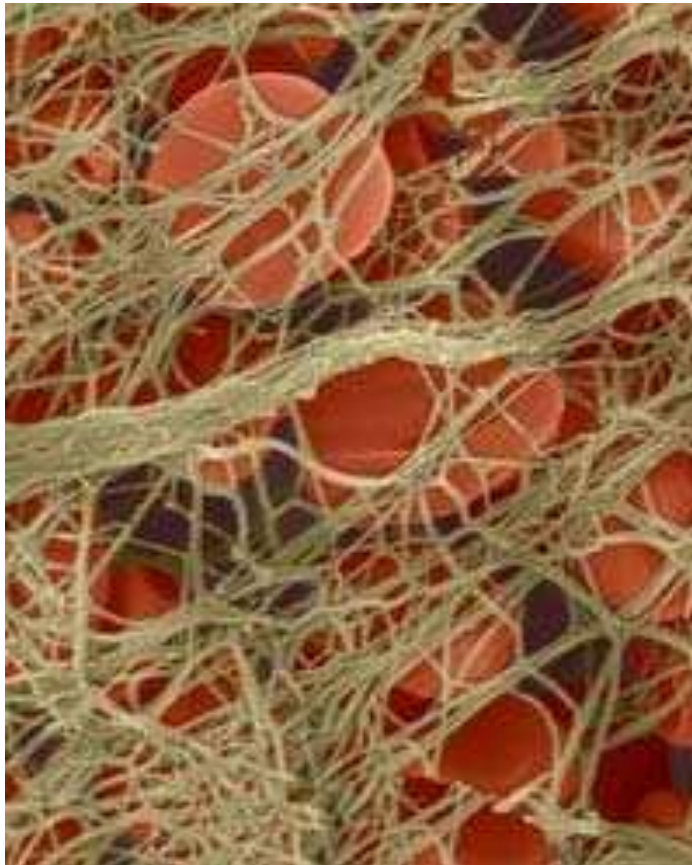
Xa + V

prothrombin -----> thrombin

v

fibrinogen-----> fibrin





Fibrin



XIIIa

Cross-linked  
fibrin

# HEMOSTASIS

- Several anticoagulant proteins help maintain the blood in a fluid state by neutralizing the activity of thrombin, including antithrombin (AT), heparin cofactor II, and  $\alpha_2$  macroglobulin.
- Protein C, protein S, and thrombomodulin inactivate FV and factor VIII (FVIII) and by their function, inhibit thrombin generation.
- Eventually, fibrinolytic factor plasminogen, when activated to plasmin by plasminogen activators (tissue plasminogen activator, urokinase), acts on the fibrin clot to dissolve it and naturally regulate the coagulation process.

# Clotting factor production

**Liver:** source of plasma clotting factors except VWF

**Factor VIII:** produced by liver & endothelium

**VWF:** endothelial cells & megakaryocytes

**Vitamin K dependent clotting factors are:**

- II
- VII
- IX
- X

# IMPORTANT!

- Quantitative or qualitative abnormalities in the activity of procoagulant factors lead to bleeding disorders, while abnormalities in the function and activity of anticoagulant proteins result in an increased risk of thrombosis.

# EVALUATION OF A BLEEDING DISORDER

History and Physical Examination

# History and Physical Examination

- The best screening test for a bleeding disorder is a comprehensive history and physical examination.
- The primary hindrance to finding such disorders is a lack of surgical challenges or trauma in the pediatric age group that can provide additional clues toward the diagnosis.



# History and Physical Examination

- Mild bleeding symptoms, such as epistaxis and easy bruising, are relatively common in children.
- The patient's age, gender, and developmental stage are important to consider when evaluating a possible bleeding disorder.

# History and Physical Examination

- The different components of the coagulation system are constantly evolving, and concentrations of coagulation proteins in the pediatric patient might not reach adult reference values until adolescence or adulthood.
- Easy bruising is a common finding in children between ages 1 and 10 years, more frequently over bony prominences such as the forehead, knees, and shins.

# History and Physical Examination

- Nonaccidental trauma is always a concern and should be considered in children with unexplained or excessive bleeding symptoms.
- Any type of bleeding in a non-mobile child should be considered to be a bleeding disorder or a result of nonaccidental trauma.

# History and Physical Examination

- Factors to consider when evaluating a bleeding disorder are:
  - the age of the patient at the time of the first episode;
  - the site, frequency, and extent of the bleeding;
  - personal history of recurrent unprovoked or spontaneous bleeding;
  - bleeding after surgical or procedural interventions;
  - family history of bleeding;
  - heavy menstrual bleeding in girls.

# History and Physical Examination

- Information on the duration must also be sought. This would indicate whether symptoms have been lifelong (since childhood) or of recent onset.
- There should be questions on any childhood history of epistaxis, umbilical stump bleeding, bleeding after circumcision, the answers to any of which would suggest inherited bleeding disorders.

# History and Physical Examination

- Any history of blood transfusion or other blood components, as well as a comprehensive review of past medical and surgical history is very important.
- Information on all operations including tooth extractions are to be listed together with any abnormal bleeding during or after surgery or poor wound healing.

# History and Physical Examination

- Drug history is of extreme importance since a wide variety of drugs affect hemostasis. The discovery of isolated thrombocytopenia in a patient who is taking several medications is a challenging clinical problem.
- It is very important to distinguish between drug induced thrombocytopenia and idiopathic thrombocytopenic purpura (ITP). In ITP, all other causes of thrombocytopenia must be excluded.

# History and Physical Examination

- Any family history of abnormal bleeding in both parents, maternal grandparents, aunts, uncles, and siblings as well as any history of consanguineous marriage (or among relatives) should be taken.
- A proper history is vital because the information gathered will ultimately guide the direction and extent of the laboratory evaluation and also help in determining how complications can be managed and prevented.



# History and Physical Examination

- A very careful family history is critical. Questions with the four “W's”, **who**, **when**, **where** and **what** are crucial.
1. **Who**: who is the patient, sex, age, race and family history?
  2. **When**: when did the bleeding occur, i.e. onset of bleeding? Is it related to drug ingestion or any underlying disorder? Did it develop after surgery or trauma?
  3. **Where** : sites of bleeding, skin, muscle etc.
  4. **What**: description of the type of bleeding.

# History and Physical Examination

- Bleeding symptoms from primary hemostatic defects such as abnormalities of platelets are characterized by easy bruising or petechiae, mucosal bleeding, and bleeding after trauma.
- Defects of secondary hemostasis such as coagulation factor deficiencies cause delayed bleeding after surgery, trauma, deep lacerations, and depending on the degree of coagulation factor deficiency, bleeding into joints, muscles, and soft tissues.

# History and Physical Examination

- During the neonatal period, oozing from the umbilical stump, prolonged oozing from heel stick or venipuncture sites, prolonged bleeding from circumcision, large cephalohematoma, and caput succedaneum without a traumatic birth history suggest a congenital bleeding disorder.
- Intracranial hemorrhage in a near-term or term neonate should raise concern about a potential congenital bleeding disorder.

# History and Physical Examination

- Other medical disorders that can cause easy bruising or bleeding should be considered.
- Ehlers-Danlos syndrome is a disorder of collagen, and patients typically present with hyperextensible joints and easy/prominent ecchymosis.
- Hemangiomas and hereditary hemorrhagic telangiectasias are vascular disorders that can present with bleeding symptoms, particularly in the airway and gastrointestinal tract.

# History and Physical Examination

- A detailed history of medications, nonprescription supplements, and complementary medications should be documented in the history.
- Some of these can cause acquired coagulation abnormalities, including aspirin, nonsteroidal anti-inflammatory drugs, and Ginkgo biloba extract.

# History and Physical Examination

- The history is followed by a careful thorough physical examination to assess the sites and severity of the bleeding and evaluate whether the bleeding is part of a systemic illness, a local anatomical defect or a haemostatic disorder.
- From the clinical assessment, one is able to assess whether:
  - (1) the bleeding is the result of a local anatomic defect or part of a systemic defect in hemostasis,
  - (2) the bleeding is due to a vascular defect, platelet abnormality or coagulation disorder, or
  - (3) the haemostatic defect is inherited or acquired.

scattered petechiae and purpura  
and large ecchymosis



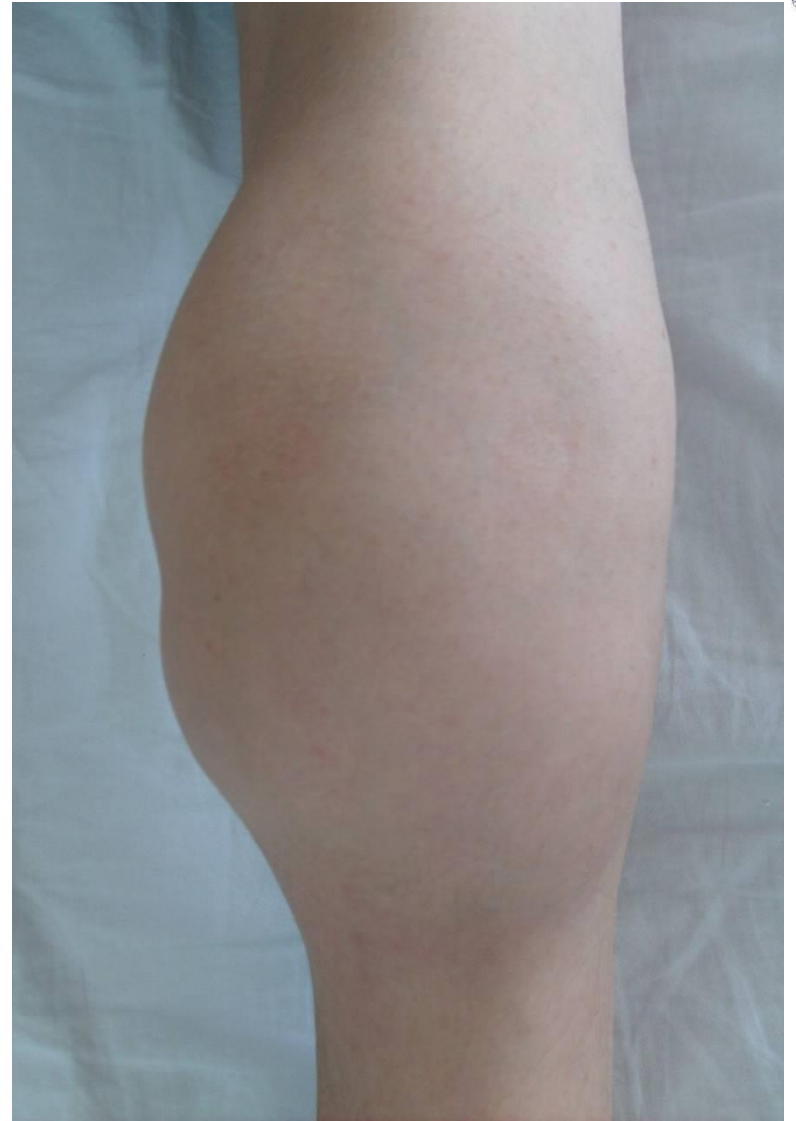






16/09/2008

# Hemarthrosis in hemophilia



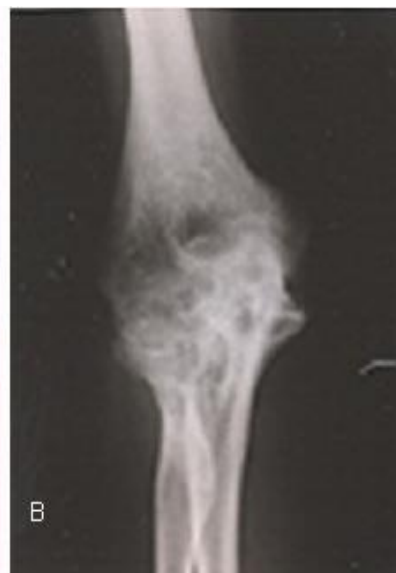


Muscle hematoma (pseudotumor)

# LONG-TERM COMPLICATIONS OF HEMOPHILIA



**Joint destruction**



**Nerve damage**



# Henoch-Schönlein Purpura



# Henoch-Schönlein Purpura



# EVALUATION OF A BLEEDING DISORDER

## Initial Laboratory Evaluation

# Initial Laboratory Evaluation

- The initial laboratory evaluation of a child with a suspected bleeding disorder should include:
  - a complete blood cell (CBC) count,
  - peripheral blood smear,
  - prothrombin time (PT),
  - activated partial thromboplastin time (aPTT),
  - fibrinogen,
  - thrombin time,
  - von Willebrand antigen and activity (vWF activity or ristocetin cofactor activity),
  - FVIII and factor IX (FIX).



# Initial Laboratory Evaluation

- The CBC count and peripheral blood smear complement each other.
- They not only provide diagnostic evidence of quantitative platelet disorders but can also assist in the evaluation of white cell and platelet morphology that can offer clues toward the diagnosis of congenital platelet disorders (eg, Döhle bodies in white cells and large platelets in May-Hegglin anomaly) or confirm the diagnosis of a malignant disorder such as leukemia.

# Initial Laboratory Evaluation

- Morphologic evaluation of red cells can exclude disorders such as a microangiopathic process that can lead to fragmented red blood cells and thrombocytopenia (eg, hemolytic-uremic syndrome/thrombotic thrombocytopenia purpura).

# Initial Laboratory Evaluation

- Prolongation of PT and aPTT in an asymptomatic child may be due to several factors.
- A common cause of prolonged clotting times is error in obtaining an adequate amount of blood or delay in processing the blood samples.

# Initial Laboratory Evaluation

- Lupus anticoagulants (LA) are often present in children after viral infections and can prolong phospholipid-dependent assays such as PT and aPTT without any bleeding consequences.
- LA cause thrombosis most commonly in patients with autoimmune disorder. In rare instances, LA can cause acquired prothrombin deficiency.

# Platelet tests

- Test platelet phase: evaluation of platelet function
- Normal (140,000 to 400,000/mm<sup>3</sup>)
- Thrombocytopenia : <140,000/mm<sup>3</sup>
- Clinical bleeding problem : <50,000/mm<sup>3</sup>
- Spontaneous bleeding with life threatening : <20,000/mm<sup>3</sup>

# Platelet tests

Test	Comment
Mean platelet volume (MPV)	Some analyzers provide MPV measurement; in healthy individuals, MPV varies inversely with platelet count
Platelet aggregation and secretion tests	Not routine tests, used only in special circumstances

# APTT

- The APTT is a test of the integrity of the intrinsic and common pathways of coagulation.
- The *in vitro* clotting time is measured after addition to plasma of calcium and the APTT reagent, which contains phospholipid (a platelet substitute, also called 'partial thromboplastin' as it lacks tissue factor), and an intrinsic pathway activator e.g. kaolin.
- The APTT should be designed to detect bleeding disorders due to deficiencies of factors VIII, IX, and XI and inhibitors of the intrinsic and common pathway factors (including lupus anticoagulant and therapeutic anticoagulants).
- Inevitably, it also detects deficiency of factor XII.

## Activated PTT (aPTT)

- Activated by contact activator (kaolin)
- Tests **intrinsic** and common pathway
- Normal ( **25-35 sec** )
- **Heparin** therapy- PTT in **50-65** sec range by promote **AT III**



# PT (Prothrombin Time)

- The PT assesses the integrity of the extrinsic and common pathways.
- The *in vitro* clotting time is measured after addition of the PT reagent, which contains thromboplastin (phospholipids with tissue factor) and calcium to citrated plasma.
- PT prolongation should detect important deficiencies (or rarely inhibitors) of factors II, V, VII and X.
- Its main use is for anticoagulant monitoring and detection of acquired bleeding disorders (especially disseminated intravascular coagulation, liver disease and vitamin K deficiency).

# PT (Prothrombin Time)

- Activated by **tissue thromboplastin**
- Tests **extrinsic** ( factor VII ) and common ( I,II,V,X ) pathways
- Normal ( **11-15 sec** )
- **Coumarin** therapy- PT at **1.5 to 2.5 time**

# PT (Prothrombin Time)

➤ **International normalized ratio (INR)**: the ratio of a patient's prothrombin time to a normal (control) sample, raised to the power of the ISI value for the analytical system used.

- (1) surgery can be done under  $INR < 3.0$
- (2) when  $INR = 3.0 - 3.5$ , consultation is needed
- (3) delay surgery when  $INR > 3.5$

# TT (Thrombin Time)

- Activated by thrombin
- Tests ability to form initial clot from fibrinogen
- Normal ( 9 to 13 seconds )

# Skin bleeding time

- This is the only *in vivo* haemostasis test available.
- It is used to test for defects of platelet-vessel wall interaction and should detect inherited or acquired disorders of platelet function, von Willebrand disease (VWD) and abnormalities of vessel wall integrity.

# Bleeding Time



# Skin bleeding time

- Duke (1910) on earlobes
- Ivy (1941) on arm with 1mm x 3mm incision
- Mielke (1969) with 1mm x 10mm template
- 1980's: disposable devices (e.g., Simplate, Surgicutt)

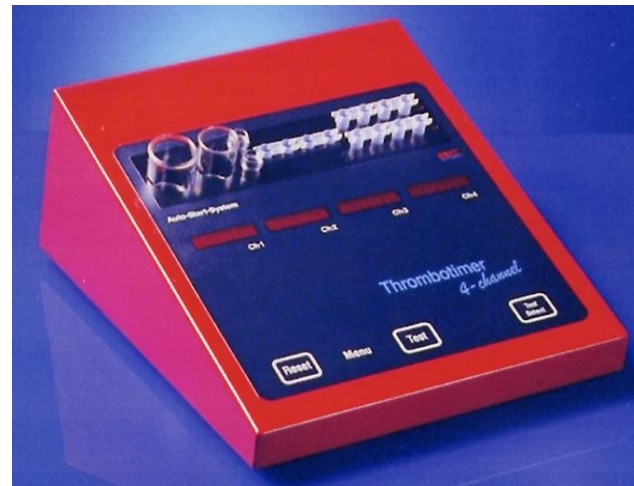
## BT (Ivy method)

- Test platelet & vascular phase
- Normal if adequate number of platelets of good quality present intact vascular walls
- Normal ( **1 to 6 minutes** )



# Other tests

- A number of tests designed to better reflect primary haemostasis and global haemostatic mechanisms have been developed.
- These include the platelet function analyser-100 (PFA-100), the thrombelastogram and measures of endogenous thrombin potential.



# Tests, Associated Abnormalities, and Differential Diagnosis

LABORATORY FINDING	DIFFERENTIAL DIAGNOSIS
PT abnormal, aPTT normal	<ul style="list-style-type: none"> <li>• FVII deficiency</li> </ul>
aPTT abnormal, PT normal	<ul style="list-style-type: none"> <li>• FVIII, FIX, FXI, FXII deficiency;</li> <li>• high-molecular weight kininogen, prekallikrein, or kallikrein deficiency;</li> <li>• severe vWD;</li> <li>• heparin effect</li> </ul>
PT and aPTT abnormal	<ul style="list-style-type: none"> <li>• FI, FII, FV, combined FV/FVIII, or FX deficiency</li> <li>• vitamin K coagulation factor deficiency</li> </ul>
No abnormalities in PT and aPTT	<ul style="list-style-type: none"> <li>• FXIII, FVIII, or FIX (mild deficiencies);</li> <li>• fibrinolytic disorders (<math>\alpha</math>-2 antiplasmin deficiency,</li> <li>• plasminogen activator inhibitor deficiency);</li> <li>• platelet function disorders</li> </ul>

# Tests, Associated Abnormalities, and Differential Diagnosis

LABORATORY FINDING	DIFFERENTIAL DIAGNOSIS
PT and aPTT prolonged with prolonged TT	<ul style="list-style-type: none"> <li>• afibrinogenemia,</li> <li>• dysfibrinogenemia,</li> <li>• DIC,</li> <li>• heparin effect</li> </ul>
PT and aPTT prolonged with normal TT	<ul style="list-style-type: none"> <li>• liver disease;</li> <li>• vitamin K deficiency;</li> <li>• FII, FV, FX deficiency;</li> <li>• DIC;</li> <li>• lupus anticoagulant;</li> <li>• warfarin effect</li> </ul>
Platelet count low	<ul style="list-style-type: none"> <li>• idiopathic thrombocytopenic purpura,</li> <li>• hereditary platelet disorder,</li> <li>• bone marrow failure syndrome</li> </ul>
Platelet function analysis (abnormal platelet function analysis)	<ul style="list-style-type: none"> <li>• vWD,</li> <li>• platelet disorder (hereditary or acquired)</li> </ul>

# Nonaccidental Trauma

- If bleeding or bruising raises concern for nonaccidental trauma, careful history, physical examination, and detailed description of physical findings are warranted.
- Bruises in areas less prone to trauma, such as the face, ears, neck, upper arms, trunk, hands, genitalia, buttocks, and anterior and medial thighs, as well as the pattern of bruises (eg, hand marks, bite marks, object marks, bruises in clusters, or large cumulative bruises) should raise concern for **child abuse**.

# Nonaccidental Trauma

- Laboratory evaluations need to be undertaken but with the understanding that the presence of a bleeding disorder or coagulation abnormality does not rule out abuse or nonaccidental trauma as an explanation for recurrent bruising or bleeding.
- If the history and physical findings disclose or provide a clear explanation for the easy bruising or bleeding, a bleeding disorder evaluation might not be needed.

# Nonaccidental Trauma

- However, in the absence of a clear explanation or findings on physical examination such as petechiae or bruising in areas of pressure to the skin (eg, bruising on the chest in areas where infant's seat fasteners-belts are applied or areas of clothing pressure), evaluation for a bleeding disorder should be considered.
- If the child presents with intracranial hemorrhage, a disseminated intravascular coagulation (DIC) panel (d-dimer and fibrinogen) in addition to the previously mentioned coagulation laboratory tests should be obtained.

THANK YOU!